

PATENT SPECIFICATION



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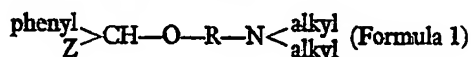
COMPLETE SPECIFICATION

Process for the Preparation of Aminoalkyl Ethers

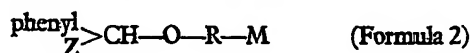
We, PARKE, DAVIS & COMPANY, a Company organized under the laws of the United States of America, of Foot of Joseph Campau at the River, City of Detroit, State of Michigan, United States of America, do hereby declare the invention for which we pray that a patent may be granted to us and the method by which it is to be performed, to be particularly described in and by the following statement:—

The present invention relates to a process for the preparation of pharmaceutically valuable compounds, according to which process amino alkyl ethers are formed with a symmetrically or unsymmetrically substituted tertiary amino group.

In its broader aspects the invention concerns the production of tertiary amino alkyl ethers having the formula:



by the alkylation of primary or secondary amines having the formula:



where M is a primary or secondary amino group, R is a divalent lower alkyl group and Z is a lower alkyl radical or a substituted or unsubstituted phenyl radical. The invention also concerns the production of primary or secondary amines of the general Formula 2 followed by alkylation thereof to the mentioned tertiary amino alkyl ethers.

As indicated, the phenyl radical represented by Z may be unsubstituted or it may be substituted by alkoxy groups or by halogen atoms, these being not only chlorine but also iodine, bromine or fluorine, whereby a certain change of the therapeutic effects becomes possible.

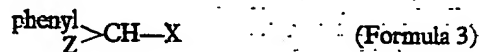
Good yields are obtained if the alkylation is carried out with formaldehyde or hexa-

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methylene tetramine in the presence of active hydrogen, or compounds evolving hydrogen, or metals evolving hydrogen, or metal alloys. It is obvious that the hydrogen may also be obtained electrolytically. It is possible, for example, for nickel in the form of Raney nickel or nickel alloys, for example Devarda alloy, to be used as metals. Metal hydrides, such as lithium-magnesium hydride, are also suitable. Finally, the alkylation may be carried out with formaldehyde in the presence of formic acid as a smooth reaction, without the formation of disturbing secondary products. By means of these alkylation methods, there are obtained substituted tertiary amino groups which contain at least one methyl group. Such substituted groups may also be obtained, if the alkylation is carried out with the aid of dimethyl sulphate in the presence of alkalis. If other dialkyl sulphates, such as, for example, diethyl sulphate, are used instead of dimethyl sulphate, there are obviously obtained the correspondingly substituted amino groups. It is also possible to effect the alkylation with the aid of mixtures of dialkyl sulphates, for example, with a mixture of dimethyl sulphate, and diethyl sulphate or another diethyl sulphate.

In particular, however, when using these working methods, it is possible, by suitable regulation of the alkylation, to obtain amino alkyl ethers with an unsymmetrically substituted tertiary amino group.

The primary or secondary amines of the general Formula 2 are obtained in accordance with the invention by condensation of α -substituted aralkyl halides having the formula



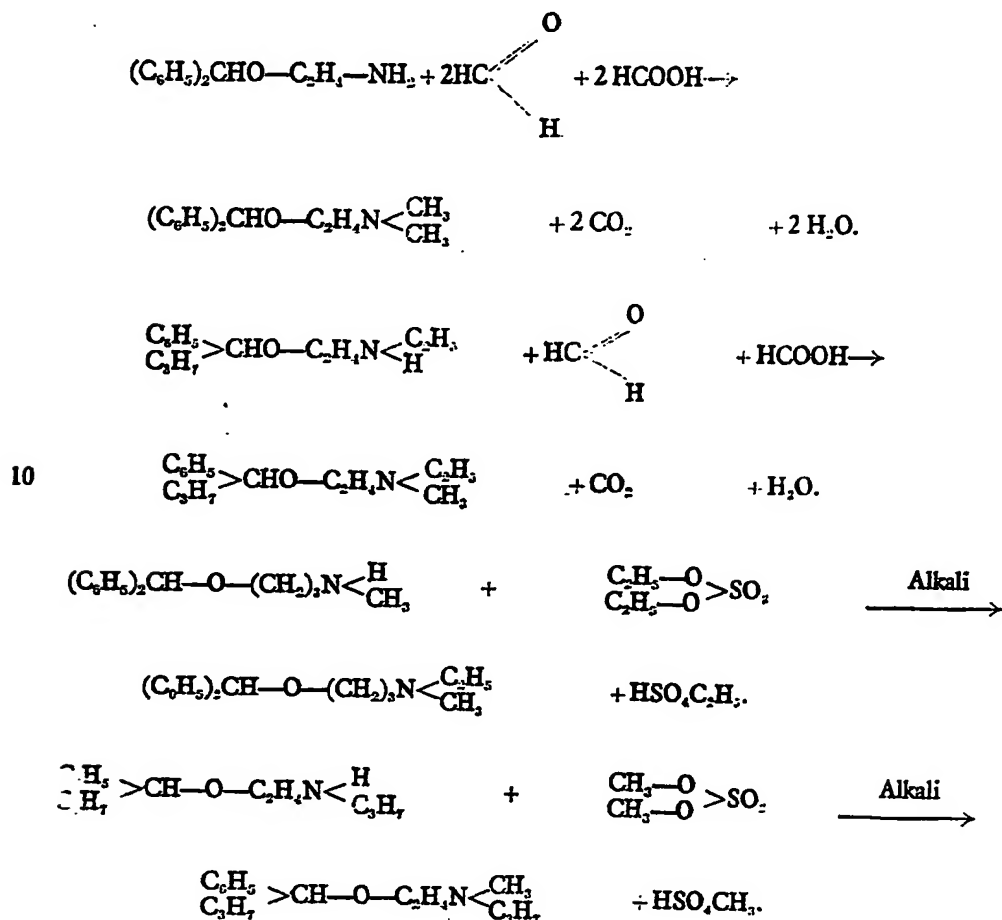
with alkali metal salts of aminoalkanols or with aminoalkanols in the presence of an acid binding agent; where X represents a halogen radical and Z has the aforementioned signifi-

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cance. They may be obtained, for example, from diphenyl bromoethane and the sodium salt of ethanolamine.

The compounds which are obtained may then be alkylated, for example, in the following manner: 5



15 It is already known to produce amine alkyl ethers by reacting secondary or tertiary alcohols of the aromatic-aliphatic series or their reactive derivatives, with amino alcohols disubstituted on the nitrogen atom, or reactive derivatives of said alcohols. By using these known processes, however, it is not readily possible for amino alkyl ethers with any desired unsymmetrically substituted tertiary amino group to be obtained, as secondary amines substituted in any desired manner are only obtainable with difficulty on a large technical scale. In accordance with previous knowledge, however, more especially from a pharmaceutical point of view, exceptional importance is attributed to the mixed amines.

30 The invention is illustrated by the following specific Examples.

EXAMPLE 1.

35 23.0 g. of sodium are added slowly to 61.1 g. of β -ethanolamine and, when the reaction is completed, the product is mixed slowly with 247 g. of diphenyl bromomethane while stir-

ring. The mixture is heated for a further two hours on a water bath, agitated with dilute hydrochloric acid and ether, the aqueous solution is mixed with caustic soda solution, the base is taken up in ether, dried with soda, the ether is distilled off and the product distilled *in vacuo*. 164 g. of the aminoethyl benzhydryl ether (about 72%) pass over at 150–153° C. at 2 mm. M.p. of the hydrochloride: 165–166° C.

227 g. of the aminoethyl benzhydryl ether thus obtained are mixed with 255 g. of 90% formic acid and 200 g. of 35% aqueous formaldehyde solution are added to this mixture. The mixture is allowed to stand for eight to twelve hours, it is then heated under reflux for four hours on a water bath; 110 c.c. of concentrated hydrochloric acid are added and the formic acid and the excess formaldehyde are distilled off. The residue is dissolved in water, the solution is filtered and mixed with 25% caustic soda solution. The base is taken up in ether and the ether is distilled off after 60

drying. The product is distilled *in vacuo* and there are obtained 200 g. of dimethyl aminoethyl benzhydryl ether (about 80%) with a b.p. of 165—167° C. at 7 mm. M.p. of the hydrochloride = 167—168° C.

EXAMPLE 2.

23.0 g. of sodium are added slowly to a solution of 89 g. methyl ethanolamine in 500 cc. toluene while stirring. After the reaction is completed, stirring is continued while 247 g. of diphenylmethylbromide dissolved in 500 cc. toluene are added dropwise and the mixture is then heated for two hours on a water-bath. After cooling the sodium bromide obtained in the reaction is separated, the base is agitated with dilute hydrochloric acid, the aqueous solution is mixed with caustic soda solution and purified by distillation.

241 g. of methyl aminoethyl benzhydryl ether are suspended in 485 cc. of 2*n*-caustic soda solution and mixed in portions with 126 g. of dimethyl sulphate while stirring vigorously. After the addition is completed, stirring is continued for a further half hour and the mixture is then heated for half an hour on a waterbath. It is allowed to cool, the aqueous layer is separated from the oily layer, the oil is taken up in ether, dried with soda, and the ether is distilled off and the product distilled *in vacuo*. 217 g. of β -dimethyl aminoethyl benzhydryl ether (about 85%) are obtained. B.p. = 165—168° C. at 7 mm.

EXAMPLE 3.

23.0 g. of sodium are added slowly to 61.1 g. of β -ethanolamine and, when the reaction is completed, the product is mixed slowly with 247 g. of diphenyl bromomethane while stirring. The mixture is heated for a further two hours on a water bath, agitated with dilute hydrochloric acid and ether, the aqueous solution is mixed with caustic soda solution, the base is taken up in ether, dried with soda, the ether is distilled off and the product distilled *in vacuo*. 164 g. of the aminoethyl benzhydryl ether (about 72%) pass over at 150—153° C. at 2 mm. M.P. of the hydrochloride: 165—166° C.

227 g. of β -aminoethyl benzhydryl ether are suspended in 984 cc. of 2*n*-caustic soda solution and 309 g. of diethyl sulphate are added while stirring. The mixture is stirred for a further half hour, and heated for half an hour on a water bath. After cooling, the oily layer is separated from the aqueous layer, the oil is taken up in ether, dried with soda, the ether is distilled off and the product distilled *in vacuo*. The β -diethyl aminoethyl benzhydryl ether distils at 160—165° C. at 2 mm. The yield is 232 g. (= 82%).

EXAMPLE 4.

23 g. of sodium are added slowly to a solution of 102 g. *n*-propyl ethanolamine in 250 cc. benzene while stirring and cooling until the sodium has entirely dissolved. Then slowly 247 g. of diphenylbromomethane dissolved in

500 cc. benzene are added dropwise, and while stirring the mixture is heated under reflux for two hours on a water bath. After cooling the sodium bromide is separated and the base is purified by distillation.

538 g. of β -*n*-propyl aminoethyl benzhydryl ether are mixed with 255 g. of 90% formic acid and 200 g. of 35% aqueous formaldehyde solution are added to the mixture. After standing for eight to twelve hours, the mixture is heated for four hours with a fitted reflux condenser on a water bath, 110 cc. of concentrated hydrochloric acid are added and formic acid and formaldehyde distilled off. The residue is treated with water, filtered and the aqueous solution is mixed with caustic soda solution. The base is taken up in ether, dried with soda, the ether is distilled off and the product distilled *in vacuo*. 442 g. of β -*n*-propyl-methyl-aminoethyl-benzhydryl ether (= 78%) with a b.p. = 158—162° C. at 4 mm. are obtained.

EXAMPLE 5.

116 g. of *n*-butyl ethanolamine and 100 g. of sodium carbonate are heated to a temperature of 60° C. and added dropwise to 247 g. of diphenylbromomethane while stirring. The mixture is stirred for a further six hours while at the same time the temperature is kept at 60—80° C. After cooling the un-transformed soda is separated with sodium bromide, the base is taken up in ether, agitated with dilute hydrochloric acid, separated from the aqueous solution by caustic soda solution and purified by distillation.

283 g. of β -*n*-butyl-aminoethyl-benzhydryl ether are suspended in 485 cc. of 2*n*-caustic soda solution and mixed with 154 g. of diethyl sulphate while stirring. The mixture is further treated as in Example 2 and there are obtained 258 g. (= 83%) of β -*n*-butyl-ethylaminoethyl-benzhydryl-ether, b.p. = 145—148° C. at 1 mm.

EXAMPLE 6.

The sodium compound is obtained from 75 g. mono-ethanolamine in 250 cc. toluene and 23 g. sodium. To this sodium compound a solution of 227 g. isobutyl-phenyl-methyl-bromide in 250 cc. toluene added under reflux while keeping the temperature at 80° C. At this same temperature the mixture is stirred for a further two hours, the sodium bromide is separated, the toluene is distilled off, and the base distilled *in vacuo*.

207 g. of this β -aminoethyl-(isobutylbenzyl) ether are suspended in 984 cc. of 2*n*-NaOH and 252 g. of dimethyl sulphate are added while stirring vigorously. Having finished this addition, the solution is stirred for a further hour, heated for half an hour on a water-bath, left to cool, the aqueous layer is separated from the oily layer, the oil is taken up in ether, dried, and the ether is distilled off and the product distilled *in vacuo*. β -dimethyl-aminoethyl-(isobutylbenzyl) ether, is obtained, b.p. = 162° C. at 10 mm.

EXAMPLE 7.

22.7 g. of β -aminoethyl benzhydryl ether obtained in accordance with the method described under Example 1 above are dissolved in 200 cc. of ethyl alcohol and 1 g. of anhydrous sodium acetate, 25 cc. of 35% aqueous formaldehyde and 58 g. of Raney nickel catalyst are added. The mixture is shaken in an Adams hydrogenation apparatus under approximately 3 atmospheres of initial hydrogen pressure until the theoretical quantity of hydrogen is absorbed. The catalyst is filtered off and the alcohol and excess formaldehyde are removed by distillation. The residue is dissolved in ether, the ether solution is washed with water and dried with potassium carbonate. The ether is removed by distillation and the desired product, β -dimethyl-aminoethyl benzhydryl ether, is obtained from the residual mixture by distillation *in vacuo*; b.p. equals 165—167° C. at 7 mm., yield 80%.

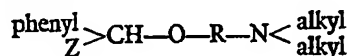
EXAMPLE 8.

135 g. of β -*n*-propylaminoethyl benzhydryl ether prepared in accordance with the method described in Example 4 above are dissolved in 500 cc. of ethanol and 5 g. of anhydrous sodium acetate, 85 cc. of 35% aqueous formaldehyde and 200 g. of Raney nickel catalyst are added. The mixture is shaken in an Adams hydrogenation apparatus under approximately 3 atmospheres of initial hydrogen pressure until the theoretical quantity of hydrogen is absorbed. The catalyst is removed by filtration and the alcohol and excess formaldehyde are removed by distillation. The residue is dissolved in ether, and the ether solution is washed with water and dried with potassium carbonate. The ether is removed by distillation and the desired product, β -*n*-propyl-methyl-aminoethyl benzhydryl ether, is obtained from the residual mixture by distillation *in vacuo*; b.p. equals 158—162° C. at 4 mm., yield 90%.

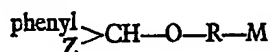
Throughout this Specification and in the appended claims, the term "lower" used in certain radicals, denotes a radical containing one to five carbon atoms.

What we claim is:—

1. Process for the production of tertiary amino alkyl ethers having the general formula



wherein primary or secondary amines having the general formula,



are reacted with a lower alkylating agent;

where M is a primary or secondary amino group, R is a divalent lower alkyl group and Z is a phenyl, substituted phenyl or lower alkyl group.

2. Process as claimed in Claim 1 wherein the alkylation is effected with formaldehyde in the presence of formic acid.

3. Process as claimed in claim 1 wherein the alkylation is effected with the aid of a dialkyl sulphate or a mixture of dialkyl sulphates in alkali medium.

4. Process as claimed in Claim 3 wherein the dialkyl sulphate is dimethyl or diethyl sulphate.

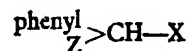
5. Process as claimed in Claim 1 wherein the alkylation of the amino group is carried out with formaldehyde or hexamethylene tetramine in the presence of active hydrogen or a compound evolving hydrogen or a metal evolving hydrogen or a metal alloy.

6. Process as claimed in Claims 1 and 5 wherein the hydrogen is evolved from a metal hydride.

7. Process as claimed in Claims 1 and 5 wherein the hydrogen is evolved by nickel, for example, Raney nickel, or metal alloys, such as Devarda alloy.

8. Process as claimed in any of the preceding claims wherein the amine starting material is a primary or secondary aminoalkyl benzhydryl ether.

9. Process for the production of tertiary amino alkyl ethers as claimed in any of the preceding claims wherein the primary or secondary amines are produced by condensation of α -substituted aralkyl halides having the formula



with alkali metal salts of aminoalkanols or the aminoalkanols in the presence of acid binding agents; where X represents a halogen radical and Z is a phenyl, substituted phenyl or lower alkyl group.

10. Process for preparing tertiary amino alkyl ethers substantially as hereinbefore described with reference to any of the specific examples.

11. Tertiary amino alkyl ethers whenever prepared or produced by the process claimed in any of the preceding claims.

12. Process as claimed in Claim 1 wherein the amino alkyl ethers are converted to salts thereof.

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